

REMARKS

1. Preliminary Remarks

a. Status of the Claims

Claims 23, 25, 31, and 33 are pending in this application. Claims 1-22, 24, 26-30, 32, and 34-38 have been previously canceled without prejudice. Claims 39 and 40 are new. Applicant respectfully request entry of the amendments and remarks made herein into the file history of the application. Upon entry of the amendments, claims 23, 25, 31, 33, 39 and 40 will be pending and under active consideration.

b. Amendment to the Claims

Claim 23 is amended in part to be directed to an isolated nucleic acid selected from the group consisting of (a) SEQ ID NO: 348, (b) a DNA encoding the nucleic acid of (a), wherein the DNA is identical in length to (a), (c) a sequence at least 80% identical to (a) or (b), wherein the sequence is 19-24 nucleotides in length; and (d) the complement of any one of (a)-(c), wherein the complement is identical in length to (a)-(c). Support for the 80% variant can be found at paragraph [0054]. Support for the length limitation of the claimed miR sequence can be found at paragraph [0050]. Support for the remaining elements of claim 23 can be found throughout the specification, as previously submitted in Applicant's reply dated March 17, 2008, for example Table 7, lines 312,839-313,772, and paragraphs [0044], [0047], and [0143-0147].

Claim 25 is amended in part to be directed to an isolated nucleic acid selected from the group consisting of (a) SEQ ID NO: 4233864, (b) a DNA encoding the nucleic acid of (a), wherein the DNA is identical in length to (a), and (c) the complement of (a) or (b), wherein the complement is identical in length to (a) or (b). Support for the amended claim 25 can be found throughout the specification, as previously submitted in Applicant's reply dated March 17, 2008, for example Table 7, lines 312,839-313,772, and paragraphs [0044], [0047], and [0143-0147].

Claims 31 and 33 have been amended in part to be directed to a vector comprising a heterologous sequence, wherein the heterologous sequence consists of the nucleic acid of claim 23 or 25. Claims 39 and 40 are new and are directed to a probe comprising a heterologous sequence, wherein the heterologous sequence consists of the nucleic acid of claim 23 or 25. Support for claims 31, 33, 39 and 40 can be found throughout the specification, for example, paragraph [0035], which is set forth below.

Accordingly, the invention provides several substantially pure nucleic acids (e.g., genomic DNA, cDNA, or synthetic DNA) each comprising a novel GAM oligonucleotide, vector comprising the DNAs, probes comprising the DNAs, a method and system for selectively modulating translation of known target genes utilizing the vectors, and method and system utilizing the GAM probes to modulate expression of GAM target genes.

Vectors are well known to be useful for many purposes, including the transfer of a nucleic acid of interest. The nucleic acid of interest is considered to be "heterologous" with respect to the basic construct of a vector. The above provided passage of paragraph 0069 of the specification clearly shows that a vector is contemplated that includes a nucleic acid of interest such as the subject matter of claims 23 or 25. One of ordinary skill in the art would recognize that features heterologous to the nucleic acid of claim 23 or 25 would be necessary for a functional vector.

Probes are well known to be useful for purpose including the hybridization and detection of a nucleic acid of interest. Hybridization is typically accomplished by using a sequence that is sufficiently complementary to the target sequence. The hybridization sequence is considered to be "heterologous" with respect to the basic construct of a probe useful for detection. The above provided passage clearly shows that a probe is contemplated that includes a hybridization sequence, such as the subject matter of claims 23 or 25. One of ordinary skill in the art would recognized that features other than the heterologous sequence would be necessary for identifying whether the probe bound to a complementary sequence.

c. Objection to the Specification

On pages 2-4 of the Office Action, the Examiner objects to the specification's reference to Tables 1-11 at paragraph [0033] and elsewhere because the Applicant is allegedly required under MPEP §608.01(p) to make a specific reference to which portions of Tables 1-10 are relied upon for support of the claimed subject matter. Applicant respectfully disagrees.

The Examiner's reference to MPEP §608.01(p) is misguided as this section is directed to incorporation of material or references from a separate U.S. patent or patent application. As shown at paragraph 0029 of the specification, the material being incorporated in Tables 1-11 was submitted on compact discs pursuant to 37 C.F.R. §1.52(e) as part of the instant application as originally filed. Therefore, Tables 1-11 are a permanent record in the file of the application and are considered part of the specification. Under 37 C.F.R. §1.52(e)(5), the specification must contain an incorporation by reference of the material on the compact disc in a separate paragraph identifying each compact disc by the name of the files contained on each compact disc, their date of creation, and their size in bytes. Applicant has complied with these rules and submits that any sequence of interest can be searched by the GAM number within the compact disc and files providing Tables 1-10. Because the incorporation of reference to Tables 1-10 via compact disc are part of the specification and in compliance with the Patent Rules, Applicant submits that the objection to the reference to Tables 1-10 in the specification is improper and should be withdrawn.

2. Patentability Remarks

a. 35 U.S.C. §101

On pages 4-14 of the Office Action, the Examiner rejects claims 23, 25, 31, and 33 under 35 U.S.C. §101 as lacking utility. The central issue is credible utility. On page 13 of the Office Action, the Examiner agrees that the claimed sequences would satisfy the specific and substantial standards of the utility requirement if the claimed sequences are capable of inhibiting a specific gene having a known function. The Examiner asserts, however, that there is no experimental evidence or verification of a single biological function, which is solely based on a computer program designed to predict miRNA-like hairpin sequences and mature miRNAs derived therefrom. The Applicant respectfully disagrees.

Specifically, the Applicant asserts that the Examiner has impermissibly applied a higher evidentiary standard for establishing utility of the claimed nucleic acids. The evidentiary standard that the Patent Office should use throughout *ex parte* examination in setting forth the utility rejection is preponderance of the totality of the evidence under consideration. A preponderance of the evidence exists when it suggests that it is more likely than not that the assertion is true. *See Herman v. Huddleston*, 459 U.S. 375 (1983). To overcome the presumption of truth of the Applicant's assertion of utility, the Examiner must establish by presenting countervailing facts that it is more likely than not that one of ordinary skill in the art would doubt (or question) the truth of the statement of utility.

With respect to claims 25, 33, and new claim 40, which are related to miR hairpin precursors, the Examiner acknowledges on page 13 of the Office Action that one of skill might reasonably believe the double stranded precursor sequence SEQ ID NO: 4233864 would enter the RNAi pathway and inhibit gene expression. Yet, the Examiner states there is no data to substantiate the function, which one of skill may require in view of the significant false-positive rates associated with bioinformatic prediction programs and the unpredictability in the art associated with enzymatic processing *in vivo*.

Applicant previously submitted the declaration of Dr. Ayelet Chajut, Ph.D. under 37 C.F.R. §1.132 (the "Chajut Declaration"), which presents experimental evidence that hsa-miR-497 (SEQ ID NO: 348) is naturally expressed and regulates the expression of human target gene uracil DNA glycosylase ("UNG") (See Supplemental Declaration dated November 25, 2008). The Examiner has erroneously rejected the evidence presented in the Chajut Declaration on the grounds that the single stranded sequence of SEQ ID NO: 348 has its own utility because the claimed miR lacks requisite properties for incorporating into the miRNA/RISC pathway, and function is asserted solely on the basis of a computer program designed to predict miRNA-like hairpin sequences and mature miRNAs.

First and foremost, the Examiner has failed to provide any evidence whatsoever to doubt that the claimed hairpin precursor would also be processed to yield a miR hairpin precursor. The Examiner's recognition that the claimed hairpin precursor is processed, but that the miR/target binding is based upon

bioinformatic prediction programs goes to the issue of miRNA/target binding predictions rather than hairpin precursor predictions, and does nothing to provide the necessary facts by a preponderance of evidence that countervails the teachings of the specification that the miR SEQ ID NO: 348 is produced by the hairpin SEQ ID NO: 4233864 and that the miR regulates UNG protein expression. The Examiner has further failed to carefully consider that the Chajut Declaration shows that hsa-miR-497 (SEQ ID NO: 348) is capable of inhibiting UNG upon delivery by a hairpin expressed in HeLa mammalian cells. Finally, even if the hairpin precursors are based upon a prediction model, the Applicant's algorithm does not violate any scientific principles and is wholly consistent with the contemporary knowledge regarding miRNA prediction algorithms and the Examiner's cited algorithm from Bentwich and Martin, which itself predict miRNA/target binding at a 61-78% success rate.¹ Accordingly, the Examiner fails to provide a greater than 50% assurance that one of ordinary skill in the art would doubt (or question) the truth of the statement of utility of the claimed hairpin related nucleic acids.

With regard to claims 23, 31, and new 39, which are related to the miR nucleic acids, the Examiner bases the rejection on miR activity depending on dsRNA intermediates and the RISC complex that are not claimed. Specifically, although the Examiner acknowledges that the data of the Chajut Declaration adequately show that hsa-miR-497 is expressed and most likely inhibits human UNG, the

¹ Applicant submits that an assertion is credible unless (A) the logic underlying the assumption is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. For example, as discussed in §2107.02 III B of the MPEP, an assertion of utility would not be considered credible where a person of ordinary skill would consider the assertion to be "incredible in view of contemporary knowledge" and where nothing offered by the Applicant would counter what contemporary knowledge might otherwise suggest. Rejections under 35 U.S.C. §101 based on lack of credible utility have been sustained by federal courts when the applicant failed to disclose any utility for the invention or asserted a utility that could only be true if it violated a scientific principle or was wholly inconsistent with contemporary knowledge in the art. See *In re Gazave*, 379 F.2d 973 (CCPA 1967).

In response to the Examiner's assertions and the stated law above, the Applicant first asserts that the Examiner has provided no evidence to countervail that hairpin SEQ ID NO: 4233864 is processed to generate miRNA SEQ ID NO: 4642, which in turn is likely to inhibit expression of the UNG protein. Whether or not the claimed polynucleotides actually exist in a biological system, and whether the true biological function of any predicted miRNA sequence has been validated according to Martin (cited by Examiner on page 7 of the Office Action) are irrelevant. The proper inquiry is instead whether a person of ordinary skill in the art would believe that the claimed polynucleotides may be used to modulate expression of the specific mRNA targets. Applicant submits evidence has been presented throughout the file history of this application.

For example, paragraph [0233] of the application discloses that the mRNA targets of the claimed polynucleotides were identified as being consistent with the free energy and spatial structure of target binding sites of known miRNAs. The method as described in paragraph [0003], [0005], [0172], and [0186] for identifying target binding sites of miRs is based upon studies at the time of filing demonstrating that miRs bind to target binding sites as disclosed in references such as Wightman *et al.* (1993), Reinhart *et al.* (2000), Slack *et al.* (2000), Lau *et al.* (2001), Lagos-Quintana *et al.* (2001), and Moss *et al.* (1997), which are all cited in the Information Disclosure Statement filed herewith. Finally, the Chajut Declaration shows that hsa-miR-497 (SEQ ID NO: 348) is capable of inhibiting UNG upon delivery by a hairpin expressed in HeLa mammalian cells.

Accordingly, Applicant's algorithm does not violate any scientific principle and is wholly consistent with contemporary knowledge regarding hairpin/miRNA prediction algorithms and the Examiner's cited algorithm from Bentwich and Martin, which itself predict miRNA/target binding at a 61-78% success rate.

data does not allegedly show the single stranded sequence of SEQ ID NO: 348 has its own utility because the claimed miR lacks requisite properties for incorporating into the miRNA/RISC pathway and the sequence is less than 100% complementary to the alleged UNG target gene.

Applicant respectfully submits that the Examiner has simply identified derivative structures and processes that may be used once an active miR has been identified. In this application, Applicant has provided and claimed the key features that provide for regulation of UNG. As a result, the claimed miR sequence (SEQ ID NO: 348) is a subcombination of miRNA/RISC complex of Cullen. A new product [or process] must be shown to be “operable”—that is, must be “capable of being used to effect the object proposed” in order to meet the utility requirement. *See Mitchell v. Tilghman* 86 U.S. 287 (1873). This does not mean, however, “that a patented device [or composition] must accomplish all objectives stated in the specification. On the contrary, subcombination claiming is consistent with the utility requirement of §101 so long as what is described in the claim has utility in itself.” *See Carl Zeiss Stiftung vs. Renishaw PLC*, 945 F.2d 1173 (Fed. Cir. 1991). Because Applicant shows the claimed miR inhibits UNG protein expression, the utility flows from this knowledge. In view of the foregoing remarks, Applicant submits that claims 23, 31, and new claim 31 have a credible utility due the utility of the subcombination claimed miR nucleic acids.

Applicant further draws attention to the Examiner that the 80% variant of SEQ ID NO: 348 has credible utility since the claimed miR sequence (SEQ ID NO: 348) does not have 100% complementary to its target sequence. Shown below is a depiction of the interaction between the miR having SEQ ID NO: 348 (top strand) and its target sequence UNG (bottom strand). This interaction is disclosed in Table 7, lines 313,569-313,572 of the application as originally filed.

| GAM NAME | GAM ORGANISM | GAM RNA SEQUENCE | TARGET BS-SEQ | TARGET | TARGET REF-ID | TARGET ORGANISM | UTR | BINDING SITE (UPPER:TARGET;LOWER:GAM) | DRAW | GAM POS |
|-----------|--------------|--------------------------------|--------------------|--------|--|-------------------------------|-----|--|---|------------|
| ===== | ===== | ===== | ===== | ===== | ===== | ===== | --- | ===== | ===== | ===== |
| GAM353678 | Human | CAGCAGCA CACTGTGG TTTGTA | CATATCTG CTGCTG | ung | NC_000907 rom 186 76 to 19335 (+) | f Haemophilus influenzae R | 3 | -- T CA ATC GT TGG AT T | ----- TGCTGCTG ACGACGAC TGTCAC | A |

The depiction shows that fifteen out of twenty-two nucleotides (68.2%) of the miR are complementary with its target sequence. As evidence by this alignment and arguments presented above, Applicant submits that sequences less than 100% identical to the miR would be expected to affect expression of the target and that the Examiner consider that part (c) of claim 23 would have credible utility. Applicant again draws the attention of the Examiner to the previous response dated November 25, 2008, wherein the data of the Chajut Declaration shows that the claimed miRNA regulates the human homolog of the above asserted target H. influenzae UNG gene. The UNG gene is highly conserved

across the evolutionary tree, from viruses to humans, as is the function of the encoded protein—so much so that human UNG can almost completely rescue the phenotype of a *ung*⁻ null-mutant strain of *E.coli*. In addition, just like the *H.influenzae* UNG mRNA, the homologous human UNG mRNA contains a hsa-miR-497 binding site, as shown below.

hsa-mir-497::H.influenzae UNG target interaction

| | | |
|---------------------|------------|----------|
| H.influenzae UNG | -- T ----- | |
| | CA ATC | TGCTGCTG |
| | GT TGG | ACGACGAC |
| hsa-miR-497 (3'>5') | AT T | TGTCAC |

hsa-miR-497::Human UNG target interaction

| | | |
|---------------------|---------------------|---------|
| Human UNG 3'UTR | CCCTAGTTTGGCG ----- | C |
| | CC | TGCTGCT |
| | GG | ACGACGA |
| hsa-miR-497 (3'>5') | TGTTT TGTCAC | C |

In view of the foregoing amendment and remarks, Applicant respectfully requests that the rejection of claims 23, 25, 31, and 33 under 35 U.S.C. §101 as lacking credible utility has been overcome and should be withdrawn.

b. 35 U.S.C. §112, First Paragraph (Enablement)

On page 4 of the Office Action, the Examiner maintained the rejection of claims 23, 25, 31, and 33 under 35 U.S.C. §112, first paragraph for allegedly failing to comply with the enablement requirement. The Examiner asserts that since the claimed invention is not supported by a credible asserted utility, one skilled in the art would not know how to use the claimed invention. Applicant respectfully disagrees.

As discussed above, the claimed nucleic acids have a credible, substantial and specific utility, namely in modulating expression of the UNG transcript, which in turn, may respectfully be useful in controlling bacterial infections. Therefore, the Applicant submits that the function of the claimed nucleic acids was known at the time of filing. In view of the foregoing remarks Applicant respectfully requests that the rejection of claims 23, 25, 31, and 33 under 35 U.S.C. §112 for lack of enablement has been overcome and therefore should be withdrawn.

c. 35 U.S.C. §102(b)

On pages 14 and 15 of the Office Action, the Examiner rejects claim 31 under 35 U.S.C. §102(b) as being anticipated by Dunn et al., GenBank Accession No. AZ593982. The Examiner asserts that the vector of Dunn comprises a sequence encoding and complementary to SEQ ID NO: 348. The Examiner also rejects claims 31 and 33 under 35 U.S.C. §102(b) as being anticipated by Birren et al, GenBank

Accession No. AC015918 (hereafter the "BAC clone"). The Examiner asserts that the BAC clone insert of Birren contains a DNA encoding instant SEQ ID NO: 4233864 and SEQ ID NO: 384.

Applicant respectfully submits that the vectors of claims 31 and 33 have inserts that are smaller in length than those disclosed in the cited references. For example, the miR insert is only 22 nucleotides in length and the hairpin insert is only 91 nucleotides in length. In stark contrast, the Dunn insert is 701 nucleotides and the BAC clone is 220,581 nucleotides in length. Thus, the Dunn insert and the BAC clone insert is far longer than the inserts of the vectors of instant claims 31 and 33, and thus do not meet the claimed length limitations. Furthermore, none of the cited §102 references teach or suggest any insert except for the Dunn insert of 701 nucleotides or the BAC clone of 220,581 nucleotides. In view of the foregoing amendment and remarks, the Applicant respectfully requests that the rejection of claims 31 and 33 under 35 U.S.C. §102(b) over Dunn or the BAC clone has been overcome and should be withdrawn.

d. 35 U.S.C. §103(a)

On pages 15-19 of the Office Action, the Examiner rejects claims 23 and 25 under 35 U.S.C. §103(a) as being unpatentable over the BAC clone in view of U.S. Patent No. 6,812,339 (hereafter "Venter"), Buck *et al.*, *Biotechniques* 27:526-538 (1999-hereafter "Buck"), U.S. Patent No. 5,541,308 (hereafter "Hogan"), and Brown, *Vet. Pathol.* 35:159-167 (1998-hereafter "Brown"). The Examiner interprets the nucleic acids of parts b and c of claim 30 to include DNA probes and sequencing primers. The Examiner contends that one of skill would have a reasonable expectation for a sequencing primer synthesized essentially anywhere along a given sequence of interest to perform adequately to yield sequence data. *Office Action*, at p. 19. The Examiner thus concludes that it would have been obvious to one of skill to synthesize a DNA identical or complementary to instant SEQ ID NO: 348 or 4233864 as a primer or probe in the process of determining the sequence of the BAC Clone. *Id.* Applicant respectfully disagrees.

With regard to SEQ ID NO: 348, Applicant submits that even if the primers cited by the Examiner include SEQ ID NO: 348 or its complement, this is not sufficient by itself to establish a *prima facie* case of obviousness. *See MPEP* § 2144.08.II ("The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness"). Considering the massive size of the genus of sequences taught by the Cited References in view of Buck, there is simply no way for one of skill to envisage the claimed subgenus of nucleic acids within the genus. *See MPEP* § 2144.08.II.a.4.(a). The BAC Clone is 220,581 nucleotides in length. Buck teaches primers of 17 to 24 nucleotides in length. *Buck*, at abstract. Accordingly, the group of 17 to 24 nucleotide-long primers cited by the Examiner that are capable of binding anywhere along the BAC Clone encompasses at least 1.76×10^6 different sequences. The claimed nucleic acid related to SEQ ID NO: 348 is but one subgenus within this huge genus of primers. There is no teaching in the Cited § 102

References or Buck to lead one of skill to select a primer that is related to a miRNA, or any other sequence capable of regulating a gene transcript in *trans*, as is provided in claim 23. The same holds true for probes—there is nothing in any of the art cited by the Examiner to lead one of skill to select a probe related to SEQ ID NO: 348 from among over one million possible sequences taught by the Cited § 102 References in view of Buck.

With regard to SEQ ID NO: 4233864, Hogan teaches that probes may be 15 to 50 nucleotides in length and at least 75% homologous to a target nucleic acid. *See Hogan*, at col. 10, line 39. Brown taught methods for making single stranded RNAs of any length less than 500 nucleotides. Accordingly, the group of 15-50 nucleotide-long probes or 91 nucleotide probes as cited by the Examiner that are capable of binding anywhere along the BAC Clone (220,581 nucleotides in length) with 100% complementarity encompasses at least 7.9×10^6 different probes. Accounting for sequences that can have as little as 75% complementarity to the BAC Clone increases the already-massive number of possible sequences to an essentially limitless amount (2.51×10^{34} probes). The claimed nucleic acid related to SEQ ID NO: 4233864 is but one subgenus within this essentially limitless genus of probes. There is no teaching in the Cited § 102 References or Hogan or Brown to lead one of skill to select a probe that is related to a miRNA precursor, or any other sequence capable of forming a miRNA, as is provided in claim 25. In view of the foregoing amendment and remarks, Applicant respectfully request that the rejection of claims 23 and 25 under 35 U.S.C. §103(a) over the BAC clone in view of Hogan, Buck, Venter and Brown has been overcome and should be withdrawn.

3. Conclusion

Applicant respectfully submits that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

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